REMARKS

Introductory Remarks

Applicants have provided herewith a Supplemental IDS to provide the Examiner with copies of all Office Actions on the merits for the following related pending patent applications: USSN 10/833,995 (VPI/00-128 RE US); USSN 10/444,588 (VPI/00-128 DIV US); USSN 10/459,420 (VPI/02-111 US); USSN 10/901,928 (VPI/02-128 CIP US); USSN 10/971,573 (VPI/02-128 CIP2 US); and USSN 10/986,569 (VPI/02-128 CIP3 US).

Applicants have also provided herewith a §1.312 declaration of Paul Charifson, Ph.D. and accompanying Exhibit A (providing comparative *S. aureus* MIC data for particular compounds) and Exhibit B (Resume/CV of Paul Charifson, Ph.D.). Also for the Examiner's convenience, applicants have also provided herewith copies of the following five cases cited hereinbelow in the section titled "The Rejections". Each case has been assigned an Exhibit number as follows:

Exhibit C: *Phillips v. AWH Corporation*, 415 F.3d 1303 (Fed. Cir. 2005);

Exhibit D: *Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007);

Exhibit E: *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990);

Exhibit F: *In re Mehta*, 52 C.C.P.A., 1615; and

Exhibit G: *Ex parte Engelhardt*, 208 USPQ 343.

The Claim Amendments

Applicants have canceled withdrawn claims 22-25 and 30-31 in order to expedite prosecution. By taking such action, applicants in no way relinquish any rights to file one or more continuing applications covering the subject matter in now canceled claims 22-25 and 30-31 or admits or acquiesces that claims 22-25 and 30-31 do not recite patentable subject matter.

Applicants have amended claims 21, 26, 28 and 32.

Applicants have amended claim 21 to depend from both claim 1 and claim 20. Support for this amendment is found at page 42, paragraph [00102].

Applicants have amended claim 26, 28 and 32 to recite specific Gram-positive bacterial species, namely *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae*. In light of the amendment discussed above, applicants have also further amended claim 28 and

32 by deleting the entire text after the phrase "b) a compound according to claim 1;" to improve their form.

None of these amendments add any new matter. Their entry is requested.

The Rejections

35 U.S.C. § 112, second paragraph

Claims 26-27 were previously rejected under U.S.C. § 112, second paragraph and the Examiner has maintained this rejection for claim 26 (claim 27 was previously canceled) for the reasons of record. The Examiner acknowledges that the claimed compounds are efficacious against the three gram positive bacteria; *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* (e.g., see the specification as filed and the §1.312 Declaration of Paul Charifson filed with applicants' August 22, 2007 Response). However, the Examiner contends that decreasing bacterial quantity does not necessarily meet the utility requirement. The Examiner concludes that "if the 'patient' of claim 26 has an increased population of gram negative bacteria, the compounds would have no utility for such scope." (emphasis is original)

Applicants disagree with the Examiner's assertions. However, in order to expedite prosecution, applicants have amended claim 26 to recite a method of decreasing *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* bacterial quantity in a patient. Moreover, applicants have provided ample support for and the Examiner has acknowledged that the presently claimed compounds are efficacious against these three bacterial species (see, page 2 of the 11/08/07 Office Action). Accordingly, applicants respectfully request that the Examiner withdraw this 35 U.S.C. § 112, second paragraph rejection.

The Examiner has also applied the rejection for "preventing a bacterial infection in a patient" from canceled claim 27 to claim 32. The Examiner asserts that the term "patient" in unclear. Specifically, the Examiner suggests that if the patient has been infected with a bacterial organism, then the "de novo prevention cannot exist and the scope of the claim is self conflicting." The Examiner concludes "[I]f the patient is not infected with the above bacteria, then, who is the patient?" Applicants traverse.

Applicants disagree with the Examiner's assertions. The term "patient" as used in the specification is clearly defined as "an animal, preferably a mammal, and most preferably a human" (see, specification at page 42, paragraph [00105]). In addition and contrary to the

Examiner's assertions, nothing within this definition or the specification suggests that a patient must have a bacterial infection. In fact, the term "patient" is commonly applied to any person seeking personal or medical services whether they have a medical condition or not. Therefore, one having ordinary skill in the art would clearly understand the metes and bounds of the claimed subject matter, especially as it relates to the term "patient". Accordingly, applicants respectfully request that the Examiner withdraw this 35 U.S.C. § 112, second paragraph rejection.

35 U.S.C. § 112, first paragraph

The Examiner has maintained the rejection of claims 26 and 28-29 under 35 U.S.C. § 112, first paragraph for the reasons of record and has added a § 112, first paragraph rejection to previously added claim 32. The Examiner previously asserted that this was a scope of enablement rejection because "no enablement support for this one bacteria activity can be extrapolated to broad spectrum 'antibacterial' activity." See Office Action of 2/22/07, page 3. The Examiner states that although the compounds of claims 26, 28-29 and 32 are efficacious against *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* bacteria, they are not enabled for a scope that encompasses all patients infected with all bacteria. Applicants traverse in part.

In order to expedite prosecution, applicants have amended claims 26, 28 and 32 to recite only *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* bacteria in the claimed methods. Moreover, applicants have provided ample support for and the Examiner has acknowledged that the compounds of the present invention are efficacious against these three bacterial species. See, page 2 of the 11/08/07 Office Action.

Additionally, the Examiner has objected to use of the term "prevention" in claim 32 suggesting that if one relies on the broadest interpretation of that term it would have to mean "ward-off of all infection" or "zero occurrence" from all bacteria. The Examiner finds this "incredible" and suggests that "even vaccines could not give such a degree of prevention." The Examiner supports her assertion by citing the Webster dictionary to then broadly interpret applicants' definition of "prevention" to suggest it means "zero occurrence." The Examiner concludes "applicants provide no factual support that the compounds, if given to post operative surgical patients, would give zero occurrence in infection of organisms: *Streptococcus*

pneumoniae, *Streptococcus pyogenes*, *Enterococcus faecalis*, *Enterococcus faecium*, *Staphylococcus aureus*, *Coag. Neg. Staph*, *Bacillus anthracis*, and *Staphylococcus epidermidis*."

As discussed above, applicants have amended claim 32 to recite a method of preventing a *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* bacterial infection in a mammal.

Furthermore, the Examiner's use of a broad interpretation of the term "prevention" to conclude that applicants mean "zero occurrence" from all bacteria in claim 32 is contrary to the way the term "prevention" is used in the antibiotic art and contrary to settled case law.

Applicants reiterate their previously presented arguments that the use of antibiotics in the prevention or prophylaxis of bacterial infections is widely accepted and known to one of skill in the art. Specifically, antibiotics are often used prophylactically before a host of surgical and dental procedures to prevent post-operative or opportunistic infections (e.g., for surgical prophylactic use of antibiotics see, http://www.intmed.mcw.edu/drug/SurgProph.html and therein the use of antibiotics prior to upper GI and elective small bowel surgery, large bowel resections, acute appendectomy, penetrating abdominal trauma, hysterectomy, prostectomy, kidney, liver and pancreas transplantations, head and neck surgery, orthopaedic surgery, etc. and for dental prophylactic use of antibiotics for patients at risk for heart infections, see http://www.qualitydentistry.com/dental/information/abiotic.html). Thus, one skilled in the art would know how to make and use the claimed invention and have the requisite assurance that the compounds of the present invention would have the asserted utility as prophylactic agents against *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* bacteria.

Further, the Examiner's reliance on the "broadest interpretation" of the Webster dictionary definition of "prevention" to refute applicants claimed method of preventing a gram-positive infection is contrary to established case law. For instance, the Federal Circuit has held "the specification is always relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of the disputed term" and that the specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Phillips v. AWH Corporation*, 415 F.3d 1303, 1321 (Fed. Cir. 2005), citing *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). Applicants' specification recites that a compound may be "administered in prophylactically effective amounts to protect individuals over an extended period of time against bacterial infections or

diseases." See page 49, paragraph [00139]. Applicants also define the phrase "prophylactically effective amount" as "an amount effective in preventing or substantially lessening a bacterial infection in a patient." See, specification at page 48, paragraph [00136]. Thus, the term "prevention" as used in applicants' specification and claim 32, suggests protection of an individual over a certain period of time from a bacterial infection. This protection does not imply "zero occurrence" from all bacterial organisms as suggested by the Examiner; rather it suggests suppression of bacterial growth sufficient to avoid a full-blown bacterial infection from the three recited gram positive bacteria.

Moreover, the definition of the term "prevent" from the dictionary would support this conclusion as well. For instance, Webster defines "prevent" to mean "to be in readiness for" or "to meet or satisfy in advance" or "taking advance measures against something possible or probable". See, *Merriam-Webster's Collegiate Dictionary* (10th ed. 1999). The Webster definition of "prevent" then suggests "taking advance measures" rather than "ward-off of all infection" or "zero occurrence" as suggested by the Examiner. Moreover, nowhere in the specification do applicants suggest prevention of a bacterial infection must mean "zero occurrence" of a particular bacteria. Rather, one skilled in the art, after reading the specification, would interpret "prevention" to mean killing or preventing the growth of enough bacteria one might be exposed to in order to prevent a full-blown systemic infection. Additionally, the Federal Circuit has stated that "a general-usage dictionary cannot overcome art-specific evidence of the meaning of a claim term." *Phillips v. AWH Corporation*, 415 F.3d 1303, 1322 (Fed. Cir. 2005), citing *Vanderlande Indus. Nederland BV v. Int'l Trade Comm'n,* 366 F.3d 1311, 1321 (Fed. Cir. 2004). Furthermore, as discussed previously, the use of antibiotics in the prevention or prophylaxis of bacterial infections is widely accepted and known to one of skill in the art. Therefore, the skilled artisan would understand that the ordinary meaning of "prevention" or prophylaxis in the antibacterial arts is as defined in the present specification rather than as "broadly interpreted" from the Webster dictionary definition. The *Phillips* court supports this type of claim interpretation. "Properly viewed, the 'ordinary meaning' of a claim term is its meaning to the ordinary artisan after reading the entire patent." *Phillips*, 415 F.3d at 1321.

In sum, applicants have demonstrated that the compounds of the present invention are efficacious against *Staphylococcus aureus*, *Enterococcus faecalis* and *Streptococcus pneumoniae* bacteria. Applicants have also provided evidence that the prophylactic use of the claimed

antibiotics to prevent post-operative or opportunistic infections is enabled for one skilled in the art. Finally, applicants have shown that case law supports their use and definition of the term "prevention" in the method of claim 32. Therefore, applicants respectfully request that the Examiner withdraw this 35 U.S.C. § 112, first paragraph rejection to claim 32 as well as the rejections to claims 26 and 28-29.

Non-statutory Double Patenting

Applicants acknowledge with appreciation that the Examiner has withdrawn the provisional obviousness-type double patenting of claims 1-21, 26, 28-29 and 32 over the claims of co-pending Application No. 10/459,420 (hereinafter "the '420 application").

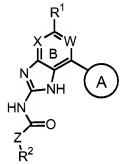
The Examiner has provisionally rejected claims 1-21, 26, 28-29 and 32 on the grounds of nonstatutory obviousness-type double patenting, as being unpatentable over claims 1-14, 19-22 of U.S. Patent No. 6,632,809 (hereinafter "the '809 patent"), unpatentable over the pending claims of co-pending Application No. 10/444,588 (hereinafter "the '588 application") and unpatentable over the pending claims of co-pending Application No. 10/833,995 (hereinafter "the '995 application"). Please note that the '809 patent, which issued on Oct. 14, 2003, is now the subject of a U.S. reissue application, the '995 application. In the '995 application, a Notice of Allowance was mailed on November 5, 2007 and the issue fee was paid on December 5, 2007. Additionally, the '588 application is a divisional of the '809 patent.

The Examiner has also provisionally rejected claims 1-21, 26, 28-29 and 32 on the grounds of nonstatutory obviousness-type double patenting, as being unpatentable over the pending claims of co-pending Application No. 10/901,928 (hereinafter "the '928 application"), unpatentable over the pending claims of co-pending Application No. 10/971,573 (hereinafter "the '573 application") and unpatentable over the pending claims of co-pending Application No. 10/986,569 (hereinafter "the '569 application") either alone or in view of the '809 patent. Specifically, the Examiner states that "although the conflicting claims are not identical, they are not patentably distinct from each other because overlapping scope are found in the co-pending claims which rendered the remaining Markush variation prima facie over each other." The Examiner states that "generically, all R1, R2 and R3 can be optionally substituted heteroaryl or heterocycle, therefore, the instant claims, genus and species are generically embraced by the issued claims." The Examiner contends that the compounds of the '809 patent are positional

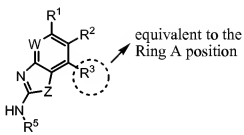
isomers of the instant compounds and states that "position isomerism for the same utility has long been recognized by the court as being structurally prima facie. (See In re Mehta 146 USPQ 284, Ex parte Engelhardt 208 USPQ 343, In re Dillon 16 USPQ2d 1897, 1911)." The Examiner concludes that the compounds of the present invention are generically embraced and rendered obvious by the teaching of each of the above-identified co-pending applications. Applicants traverse in part.

In order to expedite prosecution, applicants have filed herewith a terminal disclaimer, in compliance with 37 C.F.R. §1.321(c), to obviate the remaining obviousness-type double patenting rejections over the pending claims of the '928, '573 and '569 applications.

Regarding the '809 patent, the '995 application and the '588 application, none of these documents teaches or suggests the claimed Ring A moieties of the present invention. For instance, in the present invention, the Ring A moieties in the genus of formula I, depicted below, require a 5-6 membered heteroaryl ring wherein said ring has a hydrogen-bond acceptor in the position adjacent to the point of attachment to central Ring B (or the ortho position):



I (from the present invention)

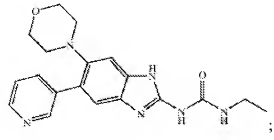


I (from the '809 patent, '995 & '588 applications)

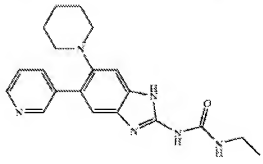
Although the equivalent position (R^3 in the genus of formula I depicted above) in the genus of formula I in each of the '809 patent, the '995 application and the '588 application can be generically heteroaryl, none of the 228 exemplified compounds contain either a direct linked aryl or heteroaryl ring in this position. Furthermore, there is no teaching in the '809 patent, the '995 application or the '588 application to suggest that if radical R^3 is heteroaryl, that it must have a hydrogen bond acceptor in the ortho position. Moreover, contrary to the Examiner's assertion, compounds 164 and 178 of the '809 patent, the '995 application and the '588 application are not positional isomers of the compounds of the instant claims. For example, in compounds 164 and 178 depicted below, the N-linked morpholine ring (e.g., cmpd 164) and the N-linked piperidine

ring (e.g., compound 178) are heterocyclic moieties in the R^2 position with a carbon (or a non-hydrogen bond acceptor atom) atom in the ortho position:

164



178



By contrast, the compounds of the present invention require an R^3 (or Ring A) heteroaryl moiety with a hydrogen bond acceptor in the ortho position. Therefore, compounds 164, 178 or any others exemplified in the '809 patent, the '995 application and the '588 application can not be fairly viewed as positional isomers of any of the compounds of the present invention.

Additionally, the combination of the claimed Ring A moieties with the claimed phenyl or 5-6 membered heteroaryl ring for R^1 is neither taught nor suggested by the genus of the '809 patent, the '995 application or the '588 application. Again, none of the 228 exemplified compounds in the '809 patent, the '995 application and the '588 application contain this required combination of substituents for the R^1 and Ring A position. Therefore, one skilled in the art would not have been motivated nor would have found it obvious to make the compounds of the present invention based on the genus described in the '809 patent, the '995 application or the '588 application.

Further, in order to establish a prima facie case of unpatentability in instances where close or established structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds, "a showing that the prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention [is] also required." See *Takeda v. Alphapharm*, 492 F.3d 1350, 1356 (Fed. Cir. 2007),

citing *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992), *In re Dillon*, 919 F.2d 688 (Fed. Cir. 1990), *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985), and *In re Lalu*, 747 F.2d 703 (Fed. Cir. 1984). "Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of a new claimed compound". *Takeda*, 492 F.3d at 1357. Nothing in the '809 patent, the '995 application or the '588 application provide such a reason.

Importantly, the combination of the claimed Ring A and R^1 moieties in the compounds of the present invention also impart surprising and unexpected antimicrobial potency against *S. aureus*. For instance, the present application recites that "applicants have discovered that the presence of the Ring A moiety, as defined above, imparts surprising and unexpectedly increased gyrase inhibitory, TopoIV activity, and antimicrobial potency." See specification at pages 12-13, paragraph [0051]). For instance, applicants have provided *S. aureus* MIC data for representative compounds of the present invention and those of the '809 patent, the '995 and '588 applications (see, Paul Charifson §1.312 declaration enclosed herewith and accompanying Exhibit A (Tables A1 and A2)). The data allows for a head-to-head comparison of the *S. aureus* MIC data (see, ¶¶ 5 and 7-8 of the Charifson declaration). Specifically, as shown in Tables A1 and A2, a comparison of the *S. aureus* (ATCC 29213 strain) MIC data for 281 compounds of the present invention shows a dramatic increase in *S. aureus* potency relative to the 60 compounds of the '809 patent, the '995 and '588 applications. Notably, 236 of 281 compounds (84%) of the present invention showed MIC activity of less than 2μg/ml whereas none of the 60 compounds (0%) of the '995 and '588 applications were in this activity range. This improved MIC data for *S. aureus* provides compelling evidence that the compounds of the present invention have enhanced antimicrobial potency relative to the '809 patent and the '995 and '588 applications.

In addition, the Examiner supports the obviousness-type double patenting rejection by suggesting that the compounds of the '809 patent are positional isomers of the instant compounds thus rendering the instant compounds *prima facie* obvious. The Examiner cites three cases to support the conclusion that "[P]osition isomerism for the same utility has long been recognized by the court as being structurally prima facie. (See *In re Mehta*, 146 USPQ 284, *Ex parte Engelhardt*, 208 USPQ 343 and *In re Dillon*, 16 USPQ2d 1897, 1911)." As discussed above, the compounds of the '809 patent are not positional isomers of the instant

compounds. Moreover, contrary to the Examiners' assertion, each of the three cited cases is distinct from and not applicable to the compounds of the present invention.

For example, in *Dillon*, the Federal Circuit upheld the Board of Patent Appeals decision "that the claims to compositions of a hydrocarbon fuel and a tetra-orthoester were prima facie obvious" over a combination of prior art references. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). The Court reached its conclusion in part because the "appellant had an opportunity to rebut the *prima facie* case" but "did not present any showing of data to the effect that her compositions had properties not possessed by the prior art compositions or that they possessed them to an unexpectedly greater degree." *Id.* at 693. In contrast, the present invention is directed to chemical compounds wherein applicants have provided compelling evidence of surprising and unexpected antibacterial activity. See Exhibit A (Tables A1 and A2) and ¶¶ 5 and 7-8 of the Charifson declaration. Therefore, unlike the appellant in *Dillon*, applicants have provided evidence of unexpected activity sufficient to rebut the Examiners' *prima facie* case.

Similarly, in *Mehta*, the Court of Customs and Patent Appeals (CCPA) affirmed the finding of the Patent Office and Board of Appeals that the appellants claimed compounds and processes were obvious in light of three prior art references. *In re Mehta*, 52 C.C.P.A., 1615. Specifically, the Court noted that appellant's compounds were exactly alike to the prior art compounds differing only in the point of attachment (e.g., 2-position vs. 3-position). *Id.* at 1621. After affirming the Boards findings that appellants' compounds were merely positional isomers, the *Mehta* Court next focused on any showing of unexpected results. The Court found no increased spasmolytic properties for appellants' compounds relative to the prior art and concluded "[W]hile a showing of significantly enhanced activity of the same general type, or a different therapeutic activity or property may constitute evidence of non-obviousness there are no showings of such type here." *Id.* at 1621. In contrast to the appellants in *Mehta* and *Dillon*, applicants have provided ample evidence of surprising and unexpected antibacterial activity. See Exhibit A (Tables A1 and A2) and ¶¶ 5 and 7-8 of the Charifson declaration. Moreover, as discussed previously, the compounds of the present invention are not mere positional isomers of any of the compounds of the prior art applications. Instead, they possess a non-obvious combination of substituents that impart surprising and unexpected antimicrobial activity.

The facts and compounds of *Engelhardt* are also clearly distinguishable from the facts and compounds of the present invention. *Ex parte Engelhardt*, 208 USPQ 343. In an appeal

from a final rejection brought before the Board of Patent Appeals and Interferences, the Board issued a new obviousness rejection under 35 U.S.C. § 103 for appellants' claims to a method of treating depression in humans using amitriptylene. *Id.* at 348. The Board noted "[A]mitriptylene is structurally different from the known antidepressant in that the nitrogen of imipramine has been replaced by an unsaturated carbon atom." *Id.* at 350. Finding enough structural similarity between the two molecules to support an obviousness conclusion, the Board next looked for a showing of unexpected properties with amitriptylene. *Id.* at 352. Similar to the stepwise analysis in both *Dillon* and *Mehta*, the Board next looked for a showing of unexpected properties with amitriptylene and concluded "the instant record does not contain sufficient evidence in this regard." *Id.* In sum, unlike the compounds in *Dillon*, *Mehta* and *Engelhardt*, the compounds of the present invention do possess surprising and unexpected activity and they differ by more than just a one atom change or a positional change of an identical substituent.

Thus, the unexpectedly better antimicrobial properties of the compounds of the instant application, and the fact that the '809 patent, the '995 and '588 applications provide no reason to select the combination of R^3 and R^1 moieties, renders the present application an unobvious, patentable invention over the '809 patent and the '995 and '588 applications. Accordingly, applicants respectfully request that the Examiner withdraw these nonstatutory double patenting rejections over the '995 and '588 applications and the '809 patent.

Conclusion

Applicants request that the Examiner enter the above amendments, consider the accompanying remarks, and allow the pending claims to pass to issue.

Respectfully submitted,

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